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Original article

Peak oxygen uptake during cardiopulmonary exercise testing determines response to cardiac resynchronization therapy

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an established treatment modality for advanced heart failure (HF) but 20–30% of patients treated with CRT do not experience clinical improvement. Hence, in this study we aimed to investigate whether baseline cardiopulmonary exercise testing (CPX) can help improve the prediction of a positive functional CRT response.
Methods: This prospective observational study included 76 HF patients undergoing elective CRT implantation and clinical CPX and echocardiographic assessment were performed at baseline, 6, and 12 months.
Results: Peak VO_2 increased from 11.0 ± 2.5 ml/min/kg to 12.0 ± 4.1 ml/min/kg and 12.2 ± 3.5 ml/min/kg at 6 and 12 months after CRT, respectively. The number of patients classified as "*CRT-responders*" (Δ peak VO_2 ≥1 ml/kg/min) was 33 (46%) and 36 (52%) at 6 and 12 months after CRT, respectively. Patients with baseline peak VO_2 <40% of predicted (lowest tertile) demonstrated a 68% and 69% response rate at 6 and 12 months, respectively, as compared to a 35% and 42% response rate among patients with baseline peak VO_2 ≥40% of predicted ($p = 0.01$ and $p = 0.02$, respectively). In multivariate analysis patients with baseline peak VO_2 <40% of predicted had an adjusted odds ratio of 4.4 (95% CI 1.6–12.5; $p < 0.01$) and 3.1 (95% CI 1.1–8.8; $p = 0.03$) for positive CRT response at 6 and 12 months, respectively.
Conclusions: Treatment with CRT improves exercise capacity but this increase is most substantial among patients with a lower baseline peak VO_2 (% of predicted). Baseline CPX can, therefore, be utilized to identify patients more likely to exhibit a functional improvement after CRT.

Introduction

Cardiac resynchronization therapy (CRT) is a relatively recent advancement in heart failure (HF) management that aims to increase cardiac output by synchronized pacing of the left and right myocardial ventricle [1,2]. It has been demonstrated that CRT can improve survival, quality of life, HF symptoms, New York Heart Association (NYHA) functional class, endothelial function as well as exercise capacity in patients with moderate to severe HF displaying evidence of ventricular dyssynchrony [3–6]. According to established guidelines, CRT should be considered in patients with electrocardiographic (ECG) evidence of dyssynchrony (QRS width ≥120 ms) with left ventricular ejection fraction (LVEF) less than 35%, in NYHA functional class III/IV and receiving optimal medical treatment regimen for HF [7]. However, despite application of these selection criteria, 20–30% of HF patients treated with CRT do not experience clinical improvement [8]. This high frequency of "non-responders" has important cost-effectiveness implications and indicates the need for more appropriate patient selection by correctly identifying patient characteristics that determine positive response to CRT therapy.

Recently, the multicenter Predictors of Response to CRT (PROSPECT) study tested the performance of the most commonly used echocardiographic parameters and found that no single echocardiographic measure could improve patient selection for CRT beyond current guidelines [9]. Cardiopulmonary exercise testing (CPX) is regarded as a functional assessment providing an

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integrated measure of both central and peripheral abnormalities, and has been shown to accurately predict hospitalization and mortality in HF patients [10–13]. Although CPX can improve significantly following CRT [2,14,15], there has been limited focus on the utility of such functional assessment for CRT patient selection. CPX is particularly useful for determining the optimal timing for heart transplantation (HTx) [16], but it is unclear whether CRT can sufficiently improve exercise capacity and, hence, allow patients scheduled for HTx to be delisted. In this prospective study we sought to (i) explore the effect of CRT on exercise capacity and on ventilatory expired gas analysis and (ii) to examine if baseline CPX could improve the prediction of a positive functional CRT response. To better understand the interaction between exercise capacity and myocardial remodeling we also evaluated the correlation between improved CPX parameters following CRT and the parallel change in traditional remodeling indices measured by echocardiography.

Methods

Patient selection

This prospective observational study included 76 consecutive stable HF patients undergoing elective CRT implantation at our tertiary center. Indications for CRT implantation were in accordance with current guidelines: (i) NYHA functional class III/IV with HF secondary to coronary artery disease (CAD) or dilated cardiomyopathy (DCM); (ii) LVEF ≤35% by any imaging method; (iii) surface ECG QRS width ≥120 ms; and (iv) optimal HF medical treatment regimen for ≥3 months [17]. Exclusion criteria were recent myocardial infarction (MI) or percutanous coronary intervention (PCI) less than 3 months before evaluation, planned revascularization, unstable and decompensated HF, severe valvular pathology other than mitral regurgitation, and previously implanted pacemakers. The study protocol was approved by the Regional Ethics Committee, complies with the Declaration of Helsinki, and written informed consent was obtained for all patients.

All patients in the current study were provided identical HF management following CRT implantation. In particular, patient medication was carefully monitored according to guidelines and side effects, and advice regarding fluid and diet intake was identical for all patients. All patients were encouraged to exercise prior to CRT implantation and no patients participated in additional rehabilitation programs.

Patient assessment and cardiopulmonary exercise testing

All patients underwent clinical assessment and blood sampling for N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement at baseline, and at 6 and 12 months following CRT implantation. Quality of life was assessed using the short form (SF)-36 questionnaire [18] and 6-min hall-walk test was performed in accordance with standard protocol [19]. Symptom limited CPX was performed using a cycle ergometer (Jaeger ER900, VIASYS Healthcare GmbH, Hochberg, Germany) and a stepwise protocol starting at 25 W with increments of 5 W per minute. Pedal speed was maintained at approximately 60 rotations per min. Before each test the equipment was calibrated using reference gases and oxygen uptake (VO_2), carbon dioxide output (VCO_2), and minute ventilation were measured on a breath-to-breath basis (MVmax 229, VIASYS Healthcare GmbH). Peak VO_2 was defined as the highest oxygen uptake recorded during the last 30 s of exercise. VE/VCO_2 slope was calculated by least square linear regression using values obtained throughout the whole exercise. Ventilatory threshold was determined using standard graphical methods. Heart rate and rhythm were continuously recorded, and brachial arterial blood pressure was measured every 2 min.

Echocardiography

Resting cardiac echocardiograms were recorded in the left lateral decubitant position using a commercially available digital ultrasound scanner (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). Images were obtained using a 2.5–3.5 MHz broadband transducer in two parasternal and three standard apical views and 2D-gray scale, color Doppler, and tissue Doppler imaging (TDI) data were obtained. Images were analyzed off-line (EchoPAC 7.0.0, GE Vingmed Ultrasound, GE Healthcare, Horten, Norway), by a single physician blinded to the patients' clinical and functional assessment data. Measurements of left ventricular (LV) dimensions were obtained according to consensus guidelines [20]. Doppler ultrasound has been shown to be a reliable and reproducible tool for assessment of interventricular delay/dyssynchrony and this was measured for all patients in the current study [21].

Quality of life

Patients participating in the study answered the Norwegian version 1.2 of the SF-36 questionnaire. Responses were related to the 4 weeks preceding the answering and scores were weighted and aggregated (into 8 dimensions) to obtain a physical component summary (PCS) and a mental component summary (MCS) score, and compared to the Norwegian population norm [18].

Device implantation

A biventricular pacemaker device was implanted using local anesthesia and with the patient in the supine position. Biventricular devices used were CRTs Contak TR2 ($n = 26$; Guidant Corp., St. Paul, MN, USA), InSync III ($n = 35$; Medtronic Inc., Minneapolis, MN, USA), and CRT-Ds (biventricular pacemaker including cardioverter-defibrillator Contak TR4 ($n = 1$; Guidant Corp.)), InSync Protect ($n = 13$, Medtronic Inc.), and InSync Marquis ($n = 1$; Medtronic Inc). No major complications were encountered during or after implantation. The day after implantation, the AV-interval was optimized for maximal diastolic filling by Doppler echocardiography using the iterative method. The interventricular pacing interval between the LV and right ventricular (RV) lead (VV-interval) was optimized using pulsed wave Doppler measurements of aortic outflow velocity time integral at different VV-intervals.

Definition of response to CRT

Peak VO_2 defines a person's functional aerobic capacity as it represents the maximal achievable level of oxygen uptake, transport, and utilization [10]. In this study Δ peak VO_2 ≥1 ml/kg/min was considered a positive response to CRT based on previous landmark trials that have established this cut-off as a functional CRT efficacy endpoint [2,15].

Transplantation listing criteria

The primary current CPX criteria for HTx listing at our center is peak VO_2 ≤12.0 ml/kg/min for patients receiving β-blockers and peak VO_2 ≤14.0 ml/kg/min for patients not receiving such therapy [16].

Table 1
Patient characteristics at baseline, 6 months, and 12 months after cardiac resynchronization therapy.

	Baseline (n = 76)	6 months (n = 71)	12 months (n = 69)
Patient demographics			
Patient age (years)	64 ± 1.1	–	–
Male gender	64 (84%)	–	–
Atrial fibrillation	16 (21%)	–	–
Etiology for CHF			
IHD	38 (50%)	–	–
Cardiomyopathy	38 (50%)	–	–
Medical therapy			
Statin therapy	42 (55%)	–	–
Beta blocker	69 (91%)	–	–
Diuretics	69 (91%)	–	–
Spironolactone	43 (57%)	–	–
NYHA class			
I	0 (0%)	2 (3%)	5 (7%)
II	0 (0%)	46 (67%)	46 (67%)
III	66 (87%)	21 (30%)	16 (23%)
IV	10 (13%)	0 (0%)	2 (3%)
NT-proBNP (pmol/L)	374.0 ± 468.9	234.5 ± 278.2	181.7 ± 212.1
QRS duration (ms)	174.3 ± 2.4	138.3 ± 2.5	135.9 ± 2.2
Quality of life			
Physical combined score	30.4 ± 8.1	38.0 ± 11.2	37.1 ± 10.5
Mental combined score	42.3 ± 10.3	47.1 ± 11.0	50.5 ± 12.1
6 min hall test (meters)	483.3 ± 99.2	–	515.8 ± 93.0
Echocardiography			
LVEF (%)	21.9 ± 7.7	27.2 ± 10.3	29.2 ± 11.3
LVESV (ml)	211 ± 99	173 ± 113	160 ± 107
LVEDV (ml)	266 ± 112	231 ± 133	212 ± 119
IVMD (ms)	59.1 ± 27.3	28.9 ± 28.4	28.8 ± 31.2
Cardiopulmonary exercise data			
Peak VO_2 (ml/kg/min)	11.0 ± 2.5	12.0 ± 4.1	12.2 ± 3.5
Peak VO_2 (l/min)	0.95 ± 0.27	1.0 ± 0.4	1.1 ± 0.4
Peak VO_2 (% of predicted)	44.8 ± 11.3	50.0 ± 16.6	51.8 ± 15.4
Watts	57.3 ± 19.8	65.3 ± 26.4	66.8 ± 27.4
Resting sinus rhythm heart rate (bpm)	70.7 ± 10.5	77.6 ± 16.4	75.0 ± 13.1
Peak sinus rhythm heart rate (bpm)	116.3 ± 28.2	114.0 ± 25.9	112.5 ± 23.0
Resting AF heart rate (bpm)	69.4 ± 14.2	81.0 ± 17.2	73.9 ± 5.6
Peak AF heart rate (bpm)	123.7 ± 30.7	107.2 ± 28.1	104.4 ± 28.4
O_2 pulse (% of predicted)	54.0 ± 16.9	61.4 ± 19.3	64.9 ± 19.1
VE peak (l/min)	49.5 ± 13.9	50.0 ± 13.3	51.5 ± 12.1
VE/VCO_2 slope	46.1 ± 8.7	44.8 ± 9.3	44.3 ± 8.3

CHF, congestive heart failure; IHD, ischemic heart disease; NYHA, New York Heart Association; NT-proBNP, N-terminal probrain natriuretic peptide; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; IVMD, interventricular motion delay; AF, atrial fibrillation; VO_2, oxygen uptake; VCO_2, rate of elimination of carbon dioxide; VE, slope of ventilation.

Statistical analysis

Analyses were performed with the SPSS statistical software (SPSS Inc. Chicago, IL, USA; v.16.0). Data are expressed as mean ± SD and a two-tailed p-value <0.05 was considered statistically significant. Student's t-test was used for normally distributed continuous variables and Mann–Whitney test for other continuous variables. Categorical variables were compared using the chi-square test. The association between baseline characteristics and the outcome "*CRT responder*" was initially evaluated by univariate analysis and significant predictors (two-tailed $p < 0.05$) were entered into a forward stepwise logistic regression analysis (continuous variables categorized according to mean/median as appropriate) with criteria for entry and exit at $p < 0.05$ and <0.10, respectively. Model performance was assessed by the Hosmer–Lemeshow goodness-of-fit test.

Results

Of the 76 patients included in this study, etiology for HF was noted to be CAD in 38 (50%) patients and DCM in 38 (50%) patients. Baseline peak VO_2 was 11.0 ± 2.5 ml/kg/min, LVEF was 21.9 ± 7.7%, and left ventricular end systolic volume (LVESV) was 211 ± 99 ml (Table 1). Of the 76 patients, 69 (91%) underwent CPX at baseline, 6, and 12 months after CRT (2 patients underwent HTx, 1 was operated for aortic stenosis, 3 died, and 1 patient was lost to follow-up).

Exercise data following CRT

CRT treatment resulted in several changes in exercise parameters (Table 1). Resting heart rate (HR) decreased significantly, but so did peak HR resulting in unchanged HR reserve. Both peak O_2 pulse, an indirect measurement of stroke volume, and peak systolic BP increased, whereas, ventilatory efficiency assessed by VE/VCO_2 slope decreased (Table 1). The number of patients classified as "*CRT-responders*" (Δ peak $VO_2 \geq 1$ ml/kg/min) was 33 (46%) and 36 (52%) at 6 and 12 months after CRT, respectively.

Improvement in exercise capacity among CRT responders and non-responders

When comparing patients classified as responders (Δ peak $VO_2 \geq 1$ ml/kg/min) versus non-responders, a significant difference in Δ peak VO_2 (2.9 ± 3.5 ml/kg/min versus −1.0 ± 2.2 ml/kg/min, $p < 0.01$), Δ peak VO_2% of predicted (14 ± 14% versus −4 ± 11%, $p < 0.01$), Δ O_2 pulse (2.4 ± 3.1 ml/beat versus 0.2 ± 3.0 ml/beat, $p < 0.01$), Δ peak HR (3 ± 28 bpm versus −15 ± 29 bpm, $p < 0.01$), Δ VE peak (5.6 ± 11.0 versus −5.3 ± 13.0, $p < 0.01$) and Δ VE/VCO_2 (−4.7 ± 8.9 versus 1.9 ± 7.2, $p < 0.01$) was observed at 6 months after

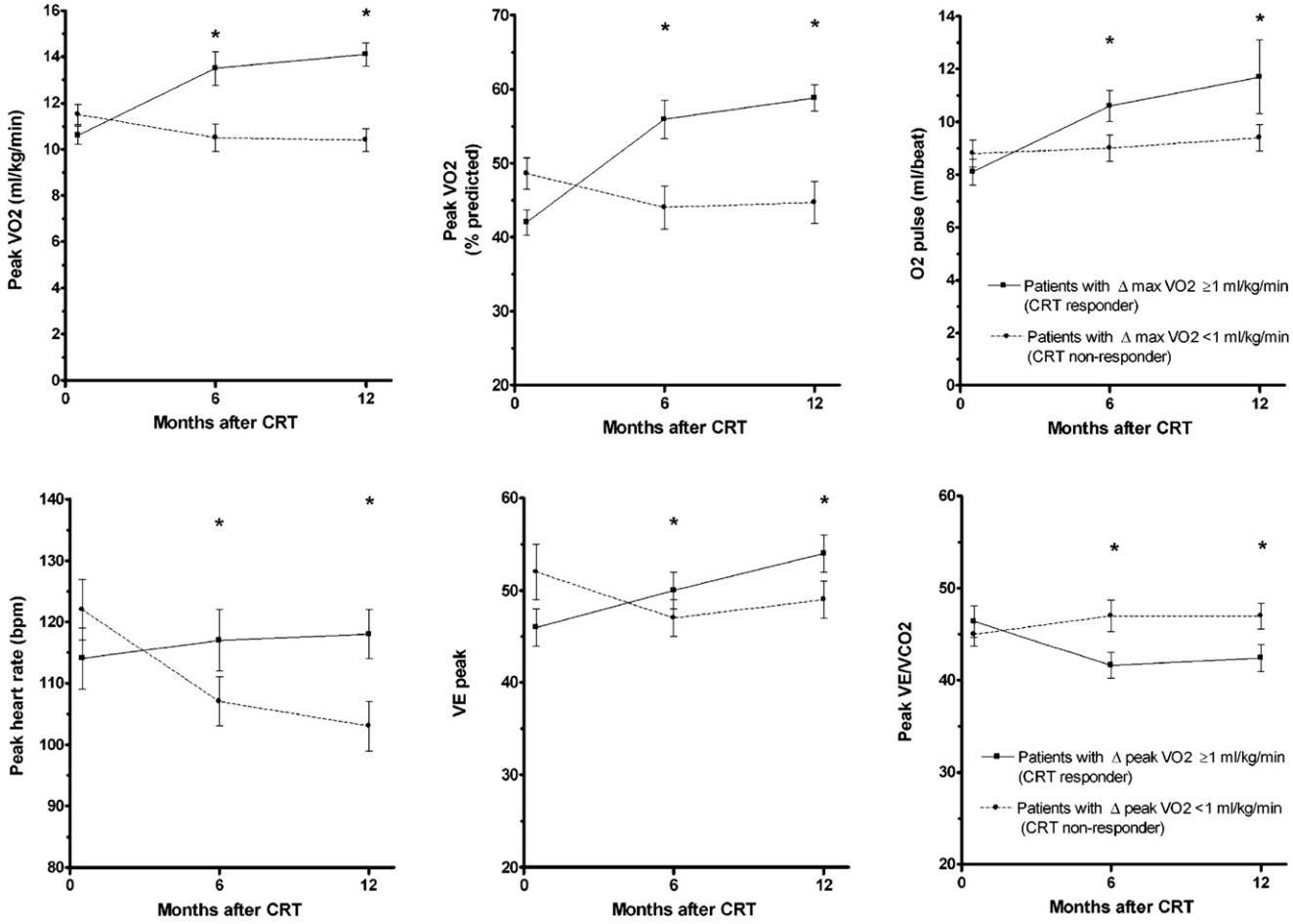

Fig. 1. Change in exercise capacity and ventilatory gas parameters among patients classified as responders versus non-responders according to increase in peak VO_2 after 12 months of cardiac resynchronization therapy (CRT) (response = Δ peak VO_2 ≥1 ml/kg/min). *Refers to $p < 0.05$ and annotates a statistically significant difference between the two groups.

CRT (Fig. 1). The observed difference in these exercise capacity parameters among responders and non-responders was maintained at 12 months after CRT (Fig. 1). Improvement in 6-min hall walking distance after 12 months of CRT was also significantly greater among patients classified as CRT responders (49.7 ± 67.6 m versus −3.0 ± 93.3 m, $p < 0.01$).

Determinants of CRT response (Δ peak VO_2 ≥1 ml/kg/min)

Baseline peak VO_2 was significantly lower among patients classified as responders as compared to non-responders after 12 months of CRT (Table 2). No significant difference in patient demographics or concomitant medical therapy for HF was noted when comparing responders versus non-responders (Table 2). Upon classification of patients into quartiles according to baseline peak VO_2 a negative linear relationship was observed with the most dramatic improvement in ventilatory capacity being evident among patients with baseline peak VO_2 ≤9.4 ml/kg/min (Fig. 2). Patients with baseline peak VO_2 <40% of predicted (lowest tertile) demonstrated a 68% response rate at 6 months after CRT initiation as compared to a 35% response rate among their counterparts with baseline peak VO_2 ≥40% of predicted ($p = 0.01$). Similarly, after 12 months of CRT, a 69% and 42% response rate was evident among patients with baseline peak VO_2 <40% and ≥40% of predicted, respectively ($p = 0.02$). Overall, during the 12-month study period a significant increase in peak VO_2 was observed among patients with baseline peak VO_2 <40% as compared to ≥40% of predicted (Δ peak VO_2 0.2 ± 0.3 l/min versus 0.07 ± 0.2 l/min, $p = 0.04$) but this did not apply to other CRT responses such as the 6-min walk test, physical combined score, LVESV, or LVEF (Fig. 3).

When evaluating baseline markers of dyssynchrony, we observed that the mean QRS duration was 175 ± 22 ms. Dyssynchrony measured by pulsed Doppler parameters showed a mean

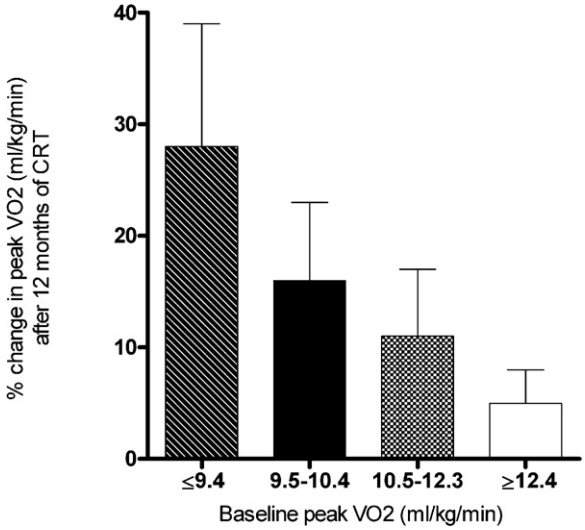

Fig. 2. Percent increase in peak VO_2 (ml/kg/min) following 12 months of cardiac resynchronization therapy (CRT) according to baseline exercise capacity (4 groups represent quartile values).

Table 2
Baseline characteristics of patients classified as responders (ΔVO_2 peak ≥1 ml/kg/min) versus non-responders (ΔVO_2 peak <1 ml/kg/min) after 12 months of cardiac resynchronization therapy.

	Responders ($n=36$)	Non-responders ($n=33$)	p-Value
Patient demographics			
Patient age (years)	63.7 ± 10.1	64.3 ± 9.7	0.78
Male gender	31 (86%)	28 (85%)	0.88
Atrial fibrillation	8 (22%)	6 (18%)	0.68
Etiology for CHF			
IHD	16 (44%)	18 (55%)	0.40
Cardiomyopathy	20 (56%)	15 (45%)	0.40
Medical therapy			
Statin therapy	17 (47%)	21 (64%)	0.17
Beta blocker	33 (92%)	29 (88%)	0.60
Diuretics	30 (83%)	32 (97%)	0.06
Spironolactone	17 (47%)	21 (64%)	0.60
NYHA class			
III	31 (86%)	30 (91%)	0.53
IV	5 (14%)	3 (9%)	0.53
NT-proBNP (pmol/L)	327 ± 324	423 ± 615	0.29
QRS duration (ms)	176 ± 20	173 ± 21	0.65
Quality of life			
Physical combined score	31.2 ± 9.3	30.7 ± 7.2	**0.01**
Mental combined score	43.4 ± 11.1	40.9 ± 9.1	0.32
6-min hall test (meters)	496 ± 84	483 ± 102	0.55
Echocardiography			
LVEF (%)	21.1 ± 7.8	22.5 ± 7.7	0.40
LVESV (ml)	211.3 ± 95.1	211.5 ± 106.4	0.99
LVEDV (ml)	263.6 ± 107.7	266.6 ± 119.5	0.92
IVMD (ms)	63.9 ± 22.5	53.5 ± 30.9	**0.04**
Cardiopulmonary exercise data			
Peak VO_2 (ml/kg/min)	10.6 ± 2.3	11.7 ± 2.4	**0.04**
Peak VO_2 (l/min)	0.9 ± 0.3	1.0 ± 0.3	0.18
Peak VO_2 (% of predicted)	42 ± 10	49 ± 12	**0.02**
Watts	56.8 ± 20.8	58.4 ± 19.8	0.67
Peak heart rate (bpm)	114 ± 29	122 ± 28	0.21
Peak systolic BP (mm Hg)	131 ± 21	133 ± 27	0.67
O_2 pulse (ml/beat)	8.1 ± 2.8	8.8 ± .3.0	0.32
O_2 pulse (% of predicted)	53 ± 17	59 ± 16	0.19
VE peak (l/min)	45.7 ± 12.1	52.5 ± 15.5	0.10
VE/VCO_2 slope	46.4 ± 9.9	45.0 ± 7.4	0.53

CHF, congestive heart failure; IHD, ischemic heart disease; NYHA, New York Heart Association; NT-proBNP, N-terminal probrain natriuretic peptide; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; IVMD, interventricular motion delay; VO_2, oxygen uptake; BP, blood pressure; VCO_2, rate of elimination of carbon dioxide; VE, slope of ventilation.
Bold values represent statistically significant values ($p<0.05$).

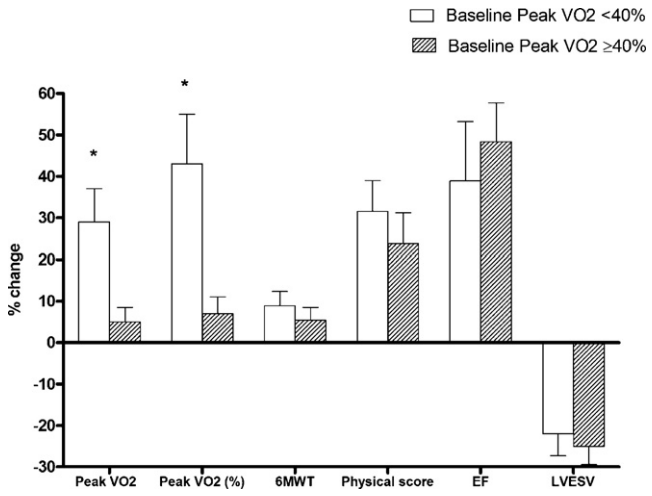

Fig. 3. Change in exercise capacity and alternative cardiac resynchronization therapy response parameters among patients with baseline peak VO_2 above and below 40% of predicted (peak VO_2 < 40% represents lowest tertile). *Refers to $p<0.05$ and annotates a statistically significant difference between the two groups as compared by ANCOVA analysis. 6MWT, 6-min hall-walk test; EF, ejection fraction; LVESV, left ventricular end systolic volume.

left ventricular pre-ejection interval (LPEI) of 182 ± 34 ms and a right ventricular pre-ejection interval (RPEI) of 125 ± 26 ms, which gives an estimated mean interventricular motion delay (IVMD) of 59 ± 28 ms. Tissue Doppler evaluation of septal-to-lateral delay was 10 ms (interquartile range 0–70). After CRT for 12 months measures of dyssynchrony in the group as a whole demonstrated a narrowing of the QRS-width to 140 ± 52 ms, LPEI was changed to 188 ± 40 ms, RPEI was found to be 164 ± 34 ms giving a reduction in IVMD to 29 ± 30 ms. Baseline mean IVMD value was noted to be significantly greater among responders than non-responders (63.9 ± 22.5 ms versus 53.5 ± 30.9 ms; $p=0.04$).

In a multivariate analysis including patient age, gender, and all baseline variables significantly ($p<0.05$) associated with CRT response at 6 or 12 months (baseline peak VO_2, interventricular motion delay, and physical combined score) patients with baseline peak VO_2 <40% of predicted had an adjusted odds ratio (OR) of 4.4 (95% CI 1.6–12.5; $p<0.01$) and 3.1 (95% CI 1.1–8.8; $p=0.03$) for positive CRT response at 6 and 12 months, respectively (Table 3). The p-values for the Hosmer–Lemeshow goodness-of-fit were 0.69 and 0.72, respectively, showing good fit of both models. It should be noted that although univariate analysis indicated that increased baseline IVMD was associated with positive CRT response, multivariate analysis revealed that this variable was only an independent predictor of positive CRT response at 6 months and not at 12 months (Table 3).

Table 3
Multivariate analysis of predictors of cardiac resynchronization therapy response (ΔVO_2 peak $\geq$1 ml/kg/min) at 6 and 12 months after device implantation.

	Response at 6 months OR (95% CI)	*p*-Value	Response at 12 months (OR 95% CI)	*p*-Value
Age (per incremental year)	1.0 (1.0–1.1)	0.18	1.0 (1.0–1.1)	0.60
Male gender	0.9 (0.2–4.2)	0.91	1.5 (0.3–6.6)	0.58
IVMD >59 ms	3.4 (1.1–10.4)	**0.03**	1.8 (0.7–5.2)	0.25
Peak VO_2 >10.4 ml/kg/min	0.7 (0.2–3.0)	0.67	1.0 (0.3–3.5)	0.96
Peak VO_2 <40% of predicted	4.4 (1.6–12.5)	**<0.01**	3.1 (1.1–8.8)	**0.03**
Physical combined score >30 points	2.7 (0.8–8.7)	0.10	0.81 (0.3–2.3)	0.69

IVMD, interventricular motion delay; VO_2, oxygen uptake.
Bold values represent statistically significant values ($p < 0.05$).

Table 4
Patients eligible for heart transplant delisting after 12 months of cardiac resynchronization therapy categorized according to baseline peak VO_2 above and below 40% predicted (criteria for listing considered as peak VO_2 <12 ml/kg/min).

	Baseline peak VO_2 <12 ml/kg/min	12 month peak VO_2 <12 ml/kg/min	Eligible for delisting
Peak VO_2 <40% of predicted ($n = 26$)	24 (92%)	14 (54%)	10 (35%)
Peak VO_2 $\geq$40% of predicted ($n = 43$)	28 (65%)	21 (49%)	7 (16%)

VO_2, oxygen uptake.

Exercise capacity improvement after CRT and corresponding change in remodeling indices

We found a modest association between Δ peak VO_2 and Δ LVESV at 6 months after CRT ($r = -0.31$, $p = 0.01$), but this association was not evident at 12 months after CRT ($r = -0.20$, $p = 0.10$). No significant association was found between Δ peak VO_2 and ΔLVEF at 6 or 12 months after CRT ($r = 0.15$ and 0.16, respectively, $p > 0.05$).

Eligibility for HTx listing/delisting following CRT

Overall, 52 (68%) of the study population was considered eligible for HTx listing using the established criteria for peak VO_2. In total, 69 patients underwent CPX testing at 12 months after CRT and 35 (51%) patients were still eligible for HTx using this criterion. We observed that a larger proportion of patients with baseline peak VO_2 <40% of predicted were eligible for HTx delisting following CRT as compared to their counterparts with baseline peak VO_2 $\geq$40% of predicted (35% versus 16%, respectively) (Table 4).

Discussion

The current study has demonstrated that exercise capacity, particularly peak VO_2, improves in patients with moderate to severe HF following CRT. We have explored the role of baseline CPX in identification of CRT functional responders and demonstrated that lower baseline VO_2 (% of predicted) is associated with a higher response rate as assessed by exercise capacity measurements. Baseline CPX can, therefore, be utilized to identify patients more likely to exhibit a functional improvement after CRT. In contrast, current studies on echocardiographic measurements do not support the use of this modality alone to determine the likelihood of CRT responses in exercise capacity, and vice versa, the improvement in exercise capacity after device implantation correlates poorly with improvements in indices of ventricular remodeling.

Overall, a considerable improvement in exercise capacity was noted in our study population together with an improvement in 6-min walk test, echo parameters (LVEF and LVESV), and quality of life assessment (combined physical score) and this is consistent with previously reported CRT studies [3,22]. Our longitudinal data demonstrated that CRT is associated with a mean improvement in VO_2, O_2 pulse, and VE/VCO_2 ratio of 9%, 15%, and 10% respectively. There are only limited studies describing the effect of CRT on exercise capacity, and it is noteworthy that our results are consistent with the findings of the landmark MIRACLE study which demonstrated a near identical level of improvement in peak VO_2 after CRT [2].

The measurement of peak VO_2 during CPX is an established risk stratification tool for patients with severe HF. This non-invasive method for characterizing cardiac reserve and functional status is also considered a reliable method for evaluating response to HF therapy. When defining a functional CRT response as Δ peak VO_2 $\geq$1 ml/kg/min [2,15], we observed a 46% and 52% response rate at 6 and 12 months, respectively. Other studies utilizing alternative measurements of CRT outcome have also reported response rates varying from 60 to 90% [23]. However, the current study has confirmed that peak VO_2 unfortunately does not increase markedly among a large proportion of patients selected for CRT, and this highlights the need for consideration of alternative patient selection protocols to help improve the likelihood of a positive CRT outcome. Indeed, our study found that a lower baseline peak VO_2 (% of predicted) was associated with a positive response to CRT at both 6 and 12 months. Multivariate analysis concluded that patients with baseline peak VO_2 <40% had a 4-fold and 3-fold higher likelihood of CRT response at 6 and 12 months, respectively. To the best of our knowledge this finding has not been reported previously and suggests the possibility of more appropriate patient selection for CRT according to baseline CPX. It should be noted that multivariate analysis did not find baseline peak VO_2 (ml/kg/min) to determine CRT response. Although these results may be interpreted as apparently contradictory, we believe it is likely to reflect the better risk stratification of peak VO_2 (% of predicted) as compared to the absolute value (ml/kg/min) which is known to be affected by a multitude of factors including age, sex, muscle mass, and conditioning status [24,25]. We also found it noteworthy that peak VO_2 (% of predicted) was a better predictor of CRT response than mechanical dyssynchrony which has previously been found to be a major determinant of clinical outcomes after CRT [26].

CPX testing is routinely performed among patients being evaluated for HTx listing and international guidelines have been published to assist appropriate patient selection based on this assessment [16]. Two previous studies have demonstrated that patients who increase their peak VO_2 on serial exercise tests have improved survival and may warrant HTx delisting [27,28]. Furthermore, the importance of HR in determining exercise capacity in CRT patients has been investigated in a recent study and it was demonstrated that chronotropic incompetence is an important determinant of peak exercise capacity [29]. With reference to

these findings, we noted a surprising decline in peak HR following CRT and this may reflect inadequate device programming. Hence, we would suggest that routine assessment of exercise capacity with particular emphasis on evaluation of HR response should be included in the management of patients selected for CRT.

Our study demonstrated that exercise capacity improved substantially with CRT, but this improvement was not correlated with the improvement in some markers of myocardial remodeling (i.e. LVEF and LVESV). Hence, our current study suggests that the change in exercise capacity is not necessarily "dependent" on LVEF or other markers of myocardial dysfunction. In fact, while myocardial remodeling is essential for the development of severe HF, several of the symptoms related to this disorder such as fatigue and dyspnea with exercise may not necessarily merely reflect the degree of myocardial failure. Furthermore, it has been suggested that these symptoms at least in part may be secondary to other mechanisms such as endocrine abnormalities, autonomic nerve dysfunction, and systemic and local (i.e. within the muscles) low-grade inflammation. Although we have no mechanistic data, our findings may further support that myocardial remodeling and development of impaired exercise capacity, at least partly, reflect separate mechanisms in the development of HF and this warrants further investigation in future studies.

This study is an observational longitudinal study and the lack of a randomized design with a control arm requires that our results be interpreted carefully. Moreover, this was not a mechanistic study, and correlations do not necessarily mean any causal relationship. Nevertheless, a relatively large number of patients were studied and our novel findings regarding the role of baseline CPX in predicting CRT response should be viewed as hypothesis-generating that require further validation in a prospective, randomized trial. It should also be borne in mind that the magnitude of a response to an intervention is often greater in patients with a greater impairment of a measure at baseline ("ceiling effect") and this could potentially have accounted for the current study results. However, it should be noted that the absolute (and not just the percentage) improvement in peak VO_2 was significantly greater among patients with baseline peak VO_2 <40%. Furthermore, a significantly larger proportion of patients with baseline peak VO_2 <40% were eligible for HTx delisting (criteria for delisting peak $VO_2 \geq 12$ ml/kg/min) confirming that this baseline parameter is a useful predictor of a functional and clinically relevant response to CRT.

Conclusions

Treatment with CRT results in improved exercise capacity but this increase is most substantial among patients with a lower baseline peak VO_2 (% of predicted). Baseline CPX can, therefore, be utilized to identify patients more likely to exhibit a functional improvement after CRT.

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